EXHIBIT 7

Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Labeling

Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

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TABLE OF CONTENTS

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Guidance for Industry[1]

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format[2]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants and reviewers in drafting the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING sections of labeling, as described in the final rule amending the requirements for the content and format of labeling for human prescription drug and biological products (21 CFR 201.56 and 201.57).[3] The recommendations in this guidance are intended to help ensure that the labeling is clear, useful, informative, and, to the extent possible, consistent in content and format.

This guidance provides recommendations on the following:

- How to decide which adverse reactions or other potential safety hazards are significant enough to warrant inclusion in the WARNINGS AND PRECAUTIONS section; what information to include when describing those adverse reactions; and how to organize the WARNINGS AND PRECAUTIONS section

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
[2] This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs.
[3] See the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," 2006, 71 FR 3922, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Note: We update guidances periodically. To make sure you have the most recent version, check the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- What situations warrant a contraindication; what information to provide in those situations when the use of the product is contraindicated; and how to organize the CONTRAINDICATIONS section
- When to include a boxed warning; and what information to include in the BOXED WARNING section

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. WARNINGS AND PRECAUTIONS SECTION (§ 201.57(c)(6))

A. Adverse Reactions That Should Be Included in the WARNINGS AND PRECAUTIONS Section

The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.[4]

Some factors to consider in assessing whether there is reasonable evidence of a causal relationship include: (1) the frequency of reporting; 2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.

1. Serious Adverse Reactions

An adverse reaction that results in any of the following outcomes should be considered serious and included in the WARNINGS AND PRECAUTIONS section:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect

[4] See the Glossary for definitions of "adverse event" and "adverse reaction."

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (§§ 312.32(a) and 314.80(a)).

2. Otherwise Clinically Significant Adverse Reactions

Adverse reactions that do not meet the definition of a serious adverse reaction, but are otherwise clinically significant because they have implications for prescribing decisions or patient management, should also be included in the WARNINGS AND PRECAUTIONS section. The following can be factors in determining whether an adverse reaction is otherwise clinically significant:

- Indication

  The relative seriousness of the disease or condition treated should be considered. For example, non-serious adverse reactions (e.g., nausea, pruritis, alopecia) caused by drugs intended to treat minor, self-limiting conditions (e.g., allergic rhinitis, cosmetic conditions, transient insomnia) may be considered clinically significant. However, those same adverse reactions caused by drugs intended to treat serious or life-threatening conditions (e.g., cancer) may be considered much less clinically significant and not appropriate for inclusion in this section.

- Incidence

  A high absolute risk or rate of occurrence of an adverse reaction can be a factor in deciding whether to include the reaction in this section.

The following types of adverse reactions could be considered otherwise clinically significant:

- An adverse reaction that may lead to a potentially serious outcome unless the dosage or regimen is adjusted, the drug is discontinued, or another drug is administered to prevent the serious outcome
- An adverse reaction that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy, and prevention or management of the adverse reaction is needed to avoid a potentially serious outcome
- An adverse reaction that can significantly affect patient compliance, particularly when noncompliance has potentially serious consequences

3. Anticipated Adverse Reactions

There are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur. The WARNINGS AND PRECAUTIONS section should include serious or otherwise clinically significant adverse reactions (as described in section II.A) that are anticipated to occur with a drug if:

- It appears likely that the adverse reaction will occur with the drug based on what is known about the pharmacology, chemistry, or class of the drug (e.g., a drug with a large QT prolongation effect would be likely to cause Torsades des Pointes arrhythmia even if no cases have yet been seen).

  OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects)

Generally, when deemed important for the prescriber, the labeling should acknowledge that the adverse reaction has not been observed with the subject drug, but may be anticipated to occur.

4. Adverse Reactions Associated with Unapproved Uses

FDA may require in the WARNINGS AND PRECAUTIONS section a discussion of an adverse reaction associated with an unapproved use if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)). The description should include a statement indicating that safety and effectiveness have not been established in that setting and that the use is not approved by FDA.

B. Risks or Other Hazards that Should be Included in the WARNINGS AND PRECAUTIONS Section

1. Laboratory Test Interference

The WARNINGS AND PRECAUTIONS section must briefly note information on any known drug interference with laboratory tests (§ 201.57(c)(6)(iv)). Interference with a laboratory test means that the laboratory test result is inaccurate because the drug interferes with the assay (e.g., a false positive or negative test result is obtained that does not accurately reflect the quantity, presence, or absence of the analyte). It does not refer to a situation in which the test result is accurate, but outside the normal range because of the physiological effects caused by the drug or its metabolites.

Only clinically significant interferences should be included. Interference with a laboratory test would be considered clinically significant if reliance on the erroneous test result would influence clinical decision-making (e.g., false positive hemoccult test).

2. Drug Interactions

The WARNINGS AND PRECAUTIONS section should briefly describe any known or predicted drug interactions with serious or otherwise clinically significant outcomes and cross-reference to any more detailed information elsewhere in the labeling (e.g., DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS, or CLINICAL PHARMACOLOGY sections).

3. Need for Monitoring to Assess Safety

The WARNINGS AND PRECAUTIONS section must identify any laboratory tests that would be helpful or necessary to identify possible adverse reactions (§ 201.57(c)(6)(iii)), or to prevent a serious adverse reaction. Information about the frequency of testing and expected ranges of normal and abnormal values should also be provided if available.

In general, information on monitoring to assess safety appears in WARNINGS AND PRECAUTIONS, and information on monitoring to assess effectiveness appears in DOSAGE AND ADMINISTRATION. In some cases, however, there may not be a clear distinction between monitoring for safety and effectiveness (e.g., cardiac monitoring to assess both safety and effectiveness in patients receiving antiarrhythmic drugs or INR testing to assess both safety and effectiveness in patients receiving warfarin), resulting in some overlap of information in WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION. Sections IIB, IIC, and IID in FDA's Dosage and Administration Final Guidance (*Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*) state that the DOSAGE AND ADMINISTRATION section of the labeling should contain monitoring information to assess both effectiveness and safety, specifically how such monitoring affects dosing of the drug (e.g., titrating the dose, modifying the dose, or discontinuing treatment).

C. Information to Provide in the Description of an Adverse Reaction

There should be a succinct description of each topic selected for inclusion in the WARNINGS AND PRECAUTIONS section. The description should cross-reference any more detailed discussion of the risk elsewhere in labeling (e.g. ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, CLINICAL STUDIES). The description should be limited to the following information, and information should be included only if known and important to clinical decision making:

- A succinct description of the adverse reaction and outcome (e.g., when the reaction occurs, whether the reaction abates over time despite continued treatment, time to resolution, significant sequelae).
- A numerical estimate of risk or adverse reaction rate[5]

[5] In characterizing overall adverse reaction experience, nonspecific terms that lack a commonly understood or precise meaning should be avoided because use of such terms can be misleading. For example, the terms *rare, infrequent,* and *frequent* do not provide meaningful information about the adverse event's frequency of occurrence.

- Known risk factors for the adverse reaction (e.g., age, gender, race, genetic polymorphism, comorbid conditions, dose, duration of use, coadministered drugs)
- Steps to take to decrease the likelihood, shorten the duration, or minimize the severity of an adverse reaction. These steps could include, for example, necessary evaluation prior to use, titration and other kinds of dose adjustment, monitoring during dose adjustment or prolonged use, avoidance of other drugs or substances, or special care during comorbid events (e.g., dehydration, infection)
- How to treat or otherwise manage an adverse reaction that has occurred

The information and advice provided should be reasonably qualified, where appropriate, to convey whatever uncertainties may exist about judgments and conclusions made (e.g., concerning causality assessments, estimated adverse reaction rates, and value of proposed monitoring).

Ambiguous and uninformative statements (e.g., use with caution) should be avoided. Instead, specific treatment or management strategies should be noted (e.g., consider lower doses or more frequent monitoring). Terminology that generally infers a contraindication (e.g., "Do not use" or "Drug X should not be used") should not appear in the WARNINGS AND PRECAUTIONS section.

D. Format

1. Individual Subsections

Each adverse reaction, syndrome, or group of reactions with a common pathogenesis (e.g., allergic contact dermatitis, maculopapular drug rash) included in the WARNINGS AND PRECAUTIONS section should have its own numbered subsection. The subsection title should accurately characterize the risk (e.g., 5.1 Thromboembolic Disorders, 5.2 Peripheral Neuropathy). When necessary, information in a subsection can be organized under non-numbered subheadings using formatting techniques such as underlining or italicizing for the subheading titles. For example, the text of a subsection entitled "5.1 Thromboembolic Disorders" can include the subheadings "Deep Vein Thrombosis" and "Thrombotic Stroke" (not "5.1.1 Deep Vein Thrombosis" and "5.1.2 Thrombotic Stroke"). Subsection headings that are not useful for signaling the content of the subsection (e.g., General) should be avoided.

2. Order of Adverse Reactions

The order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the adverse reactions. Factors to consider include the relative seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction, and the likelihood of its occurrence.

Footnote 5 continued: If categorizing adverse reactions by frequency, ranges would be helpful in understanding the drug's safety profile and the ranges should be clearly defined (e.g., occurring at a rate less than 1/100, occurring at a rate of less than 1/500).

3. Cross-Referencing

When more detailed information about an adverse reaction is included in another labeling section, the WARNINGS AND PRECAUTIONS section should cross-reference that section (e.g., ADVERSE REACTIONS, DRUG INTERACTIONS, CLINICAL PHARMACOLOGY), rather than repeat the same information. To the extent possible, redundancies should be avoided in labeling, and cross-referencing should be used instead.

4. Emphasis in Text

Bolded text or other emphasis can be used to highlight particular adverse reactions or parts of the discussion of particular adverse reactions (e.g., steps to be taken to avoid a problem, subpopulations at particular risk). Emphasis should be used sparingly so that its effect is not diminished. Thus, the entire text of a subsection in WARNINGS AND PRECAUTIONS should not be bolded; rather, bolding should be limited to only one or two sentences. Consider whether information to be emphasized should rise to the level of a Boxed Warning (see Section IV on BOXED WARNING).

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III. CONTRAINDICATIONS SECTION (§ 201.57(c)(5))

A. When to Contraindicate

A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. If there are no known contraindications for a drug, this section must state "None."

1. Observed Adverse Reactions

For observed adverse reactions, the following would ordinarily be reason to contraindicate a drug:

- The risk of the adverse reaction in the clinical situation to which the contraindication applies, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient.

  AND

- The causal relationship between exposure to the drug and the adverse reaction is well established.

2. Anticipated Adverse Reactions

Adverse reactions that are anticipated to occur when a drug is used in a specific clinical situation can be the basis for a contraindication.

Anticipated adverse reactions are distinguishable from "theoretical possibilities". Anticipated adverse reactions are supported by data (e.g., from known pharmacologic effects, class effect, chemical relationships to other drugs known to cause reactions, animal studies) and may be considered for the CONTRAINDICATIONS section. Adverse reactions based wholly on theory (theoretical possibilities) are not supported by data and would not be appropriate to include in the CONTRAINDICATIONS section.

Ordinarily, a drug should be contraindicated on the basis of an anticipated adverse reaction if the risk of the adverse reaction in the clinical situation to which the contraindication will apply, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient:

AND EITHER

- Based on what is known about the pharmacology, chemistry, or class of the drug, it appears highly likely that the adverse reaction is caused by the drug.

OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects).

The labeling should acknowledge that the adverse reaction has not yet been observed, but is anticipated to occur.

The following illustrate clinical situations for which a contraindication might be appropriate:

- Use in the presence of a comorbid condition or coexistent physiological state (e.g., existing hepatic disease, renal disease, congenital long QT syndrome, hypokalemia, pregnancy or childbearing potential, CYP 2D6 poor metabolizer[6])

- Use in the presence of a demographic risk factor, such as age, gender or other factors (e.g., contraindication in females of reproductive potential, in children below a certain age)

- Use in a defined subset of patients (e.g., people with mild disease) where the risks of the drug are such that the drug should never be used in that subset of the larger population[7]

[6] Use of a particular drug in a patient with a slow metabolizer status would be contraindicated only in situations where the dose of the drug could not be adequately adjusted.

[7] The INDICATIONS AND USAGE section must contain information about use of the drug when safety considerations are such that the drug should be reserved for certain patients (e.g., patients with severe disease) or situations (e.g., patients refractory to other drugs) (§ 201.57(c)(2)(i)(B) and (E)). In rare cases, when the risks of the drug clearly outweigh any possible therapeutic benefit and the drug should never be used in a selected patient subset, a contraindication for use of the drug in that subset should also be described in the CONTRAINDICATIONS section.

- Use with coadministered drugs where the combination is dangerous (e.g., MAO inhibitor with a tricyclic antidepressant; a drug known to prolong the QT interval with a drug known to interfere with the metabolism of that drug)

- Use of a drug in patients with known hypersensitivity when severe hypersensitivity reactions have been observed to occur with the drug.

  A contraindication in patients with hypersensitivity reactions should be included in labeling only when there are demonstrated cases of hypersensitivity with the product or such reactions may be anticipated based on data from similar drugs (e.g., those in the same pharmacological class or with similar chemical structures, or when cross-sensitivity within a class is a recognized phenomenon). When the risk of using the drug in a patient at risk for such a reaction outweighs the potential benefits (i.e., it would be clinically inappropriate to rechallenge a patient with a history of a hypersensitivity reaction to the drug or a similar drug), a contraindication to use in such patients should be included. Along with the contraindication statement, the labeling should briefly describe the type and nature of the observed (or anticipated) reaction(s), and cross-reference to a more detailed discussion elsewhere in the labeling, as appropriate.

  For example:

  DRUG-X is contraindicated in patients with a history of a hypersensitivity reaction to [active ingredient]. Reactions have included anaphylaxis and anaphylactoid reactions *[see Adverse Reactions (6.2)]*.

  If no such hypersensitivity reactions as noted above have been observed or are unlikely to occur based on the drug's characteristics, no contraindication for hypersensitivity reactions will be included.

Contraindications based on drug interactions with serious outcomes should be described briefly in the CONTRAINDICATIONS section and cross-referenced to more detailed information in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections.

B. Information to Provide

Contraindications should be worded using precise language, e.g., “Drug X is contraindicated in patients with condition Y” (instead of “Drug X should not be used in patients with condition Y”). If a drug has more than one contraindication, use an introductory statement (e.g., "Drug X is contraindicated in:") followed by a bulleted list identifying each contraindication.

For each listed contraindication, provide the following information:

- Brief description of the contraindicated situation or scenario, including any pertinent demographic or identifiable predisposing characteristics

- Description of observed or anticipated consequences of the contraindicated use

C. Format

1. Bulleted list

If a drug has more than one contraindication, FDA recommends that each contraindication be identified in a bulleted list.

2. Order of Contraindications

The order in which contraindications are presented should reflect the relative clinical significance of the listed contraindications. Factors to consider include the severity of the risk and the likelihood of occurrence.

IV. BOXED WARNING (§ 201.57(c)(1))

A. When to Use a Boxed Warning

A boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug

  OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

  OR

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 “Approval with restrictions to assure safe use” or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies” Elements to assure safe use).

Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it warrants inclusion in a boxed warning.

Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate.

For example, a contraindication to use during pregnancy based on evidence in humans or animals that drugs in a pharmacologic class pose a serious risk of developmental toxicity during pregnancy would usually be in a boxed warning for all drugs in that class, even those in which the adverse reaction has not been observed.

A boxed warning can also be considered for a drug that poses risk–benefit considerations that are unique among drugs in a drug class (e.g., to note when a drug is the only one in its class to have a particular risk and is indicated as second line therapy because of that risk).

B. Information to Provide

A boxed warning provides a brief, concise summary of the information that is critical for a prescriber to consider, including any restriction on distribution or use. There is typically a more detailed discussion of the risk elsewhere in the labeling (e.g., in CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections), that must be identified by a cross-reference (§ 201.57(c)(1)).

C. Format

The BOXED WARNING section in the full prescribing information must be formatted in accordance with § 201.57(d). The information in the boxed warning should be in bold print and presented in a bulleted format or some alternative format, such as the use of subheadings, that helps to make the information visually accessible.

GLOSSARY

Adverse Reaction (21 CFR 201.57(c)(7)): For purposes of prescription drug labeling and this guidance, an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical bodily function, such as vital signs and electrocardiogram (ECG).

Adverse Event: For the purposes of this guidance, an *adverse event* refers to any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Reaction: For purposes of this guidance, the term *serious adverse reaction* refers to any event or reaction that results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.